

UNDERSTANDING FEMALE PELVIC FLOOR DISORDERS: A CLOSER
LOOK AT THE ETIOLOGY OF PELVIC ORGAN PROLAPSE AND THE
EFFICACY OF SACRAL NEUROMODULATION FOR THE TREATMENT OF
REFRACTORY URINARY URGENCY AND FREQUENCY, AND URINARY URGE
INCONTINENCE

A Thesis

by

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ABSTRACT

The objectives of the research are to test the hypothesis that pelvic outlet diameter (POD) is associated with pelvic organ prolapse (POP) in squirrel monkeys, and to measure long-term satisfaction of women treated with sacral neuromodulation (*InterStim*®) for refractory urinary urge incontinence, urinary urgency, and frequency. Magnetic resonance images (MRI) were obtained from 55 females with and without POP. Associations of age, parity, and body weight to POD were evaluated with linear regression analysis, while relationships between age, parity, and POD with POP were examined with multiple regression analysis. Women who were at least 3.3 years remote from *InterStim*® implantation were contacted by telephone to assess treatment satisfaction (Likert-type scale), symptom severity (UDI-6), disease related quality of life (IIQ-7), and patient global impression of improvement (PGI).

Pelvic outlet diameter was not related to parity ($p = 0.10$) or weight ($p = 0.053$), but was inversely related to age. ($p = 0.011$) Animals with POP did not differ from those without POP in age ($p = 0.10$), weight ($p = 0.17$), or POD ($p = 0.99$). The groups differed in parity ($p = 0.007$) and multiple regression methods demonstrated that only parity had a significant relationship with POP ($p = 0.002$). In measuring long-term satisfaction of those treated with sacral neuromodulation, 37.5% of respondents were “satisfied” with their *InterStim*® and 50% would have the procedure again. Satisfied subjects were found to be younger than dissatisfied subjects ($p = 0.10$), and reported a median improvement in their bladder symptoms of 50%. Objective incontinence

parameters and survey scores performed preoperatively and improvement during test stimulation were not predictive of long-term patient satisfaction. In conclusion, POD size does not contribute to POP in squirrel monkeys. Of the 24 subjects who were available for follow-up after 51 months of treatment, 50% would have *InterStim*® again.

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NOMENCLATURE

ANOVA	One-Way Analysis of Variance
CT	Computed Tomography
FDA	Food and Drug Administration
FPMRS	Female Pelvic Medicine and Reconstructive Surgery
FSLP	First Stage Lead Placement
IIQ-7	Incontinence Impact Questionnaire-Short Form
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
IV	Intravenous
MRI	Magnetic Resonance Imaging
OAB	Overactive Bladder
PGI	Patient Global Impression of Improvement
POD	Pelvic Outlet Diameter
POP	Pelvic Organ Prolapse
ROC	Receiver Operator Curve
SEM	Standard Error of Mean
SNS	Sacral Nerve Stimulation
UDI-6	Urogenital Distress Inventory-Short Form

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CHAPTER I

INTRODUCTION AND LITERATURE REVIEW

Pelvic floor disorders consist of urinary incontinence, fecal incontinence, and pelvic organ prolapse. A recent series of cross-sectional national health surveys estimates that 25% of adult U.S. women suffer from at least one pelvic floor disorder (1). By subtype, this includes 17% of women with urinary incontinence, 9.4% of women with fecal incontinence, and 2.9% of women with symptomatic pelvic organ prolapse. In addition, the proportion of women experiencing at least one pelvic floor disorder increases with age from 9.7% of women ages 20 to 39 to 36.8% of women ages 60-79, and 49.7% of women over the age of 80 (2). Pelvic floor disorders clearly pose a public health challenge as census data predicts a demographic increase in the number of elderly women (3).

I.1 Pelvic Organ Prolapse

In order to meet the future clinical demands of preventing, diagnosing and treating pelvic floor disorders, medical research will have to build upon what is known about the etiology and in particular risk factors and pathophysiology. The etiology of pelvic organ prolapse is multifactorial and includes advancing age, parity (in particular vaginal childbirth), obesity, previous surgery (hysterectomy, Burch colposuspension), and genetic factors (4-7). These risk factors have also been described as predisposing,

inciting, promoting, and decompensating (7). Established risk factors include increasing age, higher gravity and parity (in particular vaginal births) and obesity (5, 6). Potential risk factors are more diverse and include a multitude of factors such as obstetrical history (regardless of route of delivery), previous hysterectomy (especially if indication was for prolapse) smoking, ethnicity, and shape or orientation of the bony pelvis.

The relationship between the bony pelvis and pelvic floor disorders has been studied in humans to various degrees (8, 9). For example, a case-controlled study of women who underwent magnetic resonance imaging (MRI) of the pelvis found that a wide transverse inlet and narrow obstetrical conjugate were associated with pelvic floor disorders, duplicating results seen in a control group of women who underwent computed tomography. The authors then concluded that these particular pelvic dimensions (wide transverse inlet and narrow obstetrical conjugate) predispose women to traumatic childbirth and subsequent development of pelvic floor neuromuscular changes that results in pelvic organ prolapse.

The authors of the first study utilize the squirrel monkey as an experimental model in order to expand previous research associating bony pelvis dimensions and the development of pelvic organ prolapse. The squirrel monkey shares several characteristics with humans that make them useful for studying pelvic organ prolapse (10, 11). For example, fifty percent of older female squirrel monkeys demonstrate pelvic support defects (10), and like humans, these pelvic support defects are associated with childbirth and aging (11). Because squirrel monkeys deliver large infants (14% of maternal body weight) relative to maternal size, they are susceptible to pelvic floor

injury secondary to labor dystocia, just like their human counterparts. By using a cohort of female squirrel monkeys with known obstetrical histories across various ages the authors assess the association between pelvic outlet diameter and pelvic organ prolapse in the squirrel monkey. Conclusions from this study will further characterize the squirrel monkey as an animal model for studying human pelvic organ prolapse.

I.2 Urinary Incontinence and Overactive Bladder

Urinary incontinence is defined as “the complaint of any involuntary leakage of urine” (12). It is classified by the symptoms or events that occur during the leakage. Two prominent classifications of urinary incontinence are *stress urinary incontinence*, which is the “complaint of involuntary loss of urine on effort or physical exertion (e.g. sporting activities) or on sneezing or coughing, and *urgency (urinary) incontinence*, which refers to a “complaint of involuntary loss of urine associated with urgency”. Urinary incontinence constitutes a significant health problem in women, as a cross-sectional analysis of non-pregnant women determined approximately 15.7% of women experienced moderate or severe urinary incontinence (2). Prevalence rates will depend on the severity of leakage, with higher reported rates representing mild disease and lower rates representing more severe variants.

Like pelvic organ prolapse, urinary incontinence is more prevalent in the female gender and advancing age. The relationship between age and urinary incontinence is not linear, but rather bimodal, with the first peak onset occurring between ages 40-60, with

the second prevalence increase occurring after age 65 (13). The effect of childbirth on the prevalence of urinary incontinence has been demonstrated in young and middle age women (< age 50) but less so in older women (14). A cross-sectional study of Norwegian women demonstrated that the effect of 2 or more deliveries on urinary incontinence was greatest in younger women aged (ages 20-34 years) (15). Interestingly, this effect of childbirth was decreased among women ages 35-64, and not associated with urinary incontinence in women older than 65 (15).

Overactive bladder (OAB) is considered to be a clinical diagnosis defined as “urinary urgency, usually accompanied by frequency and nocturia (waking up from sleep in order to urinate), with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology (12, 16). The overall prevalence in the United States among females, according to a national telephone survey using clinically-validated questionnaires of non-institutionalized adults and was representative of the population in terms of sex, age, and geographical region, is 16.9% (17). The prevalence also increases with age from 2.0% to 19% with a significant increase after 44 years. Total costs of OAB in the USA was estimated to be \$65.9 billion in 2007, 22.1 % of which was accounted for by indirect costs (18).

For patients who have failed first (behavioral therapy) and second line treatments (pharmacologic management) for overactive bladder and urinary urge incontinence, neuromodulation, in particular sacral nerve stimulation (SNS), may be offered to carefully selected patients (16). Sacral nerve stimulation is an FDA-approved treatment for overactive bladder and urinary incontinence that has demonstrated the ability to

significantly improve patient quality of life and urinary symptoms as measured by both subjective and objective criteria. It involves stimulation of the pelvic plexus and pudendal nerves that innervate the bladder, pelvic floor muscles and rectum (14), and has been available in the United States since 1997 and in Europe since 1994 (19). Current FDA-approved indications for SNS include urinary urge incontinence, urgency-frequency, non-obstructive urinary retention, and most recently (2011), fecal incontinence.

The sacral neuromodulation procedure known as *InterStim®* (*Medtronic, Inc., Minneapolis, MN*) is performed in two stages (14, 19), both of which are performed in an outpatient surgery setting. Stage 1 involves placing a permanent quadipolar lead wire adjacent to a sacral root (typically S3), under fluoroscopic guidance. The patient then undergoes a test phase for 7-14 days. This period is essentially a clinical trial where the patient will monitor his or her urinary symptoms. If he or she demonstrates greater than 50% level of improvement in their symptoms by either subjective and/or objective parameters, they will then proceed to the Stage II procedure. The Stage II procedure involves the implantation of a subcutaneous pulse generator (figures 7, 8, 9, 10).

Literature reporting clinical outcomes for the treatment of urinary incontinence, overactive bladder, and other pelvic floor disorders may use any one or a combination of domains including the subject's own assessment of their symptoms, an objective quantification of symptoms, findings from a clinician's observations or exam, the patient's perceived quality of life, and any socioeconomic measures(14). A prospective analysis of patients who underwent SNS for the treatment of urgency (urinary)

incontinence showed a significant improvement in quality of life up to 36 months following implantation (20). Van Kerrebroeck et al (21) used data from patient voiding diaries to determine long-term outcomes from a 5 –year multicenter prospective trial. Clinical success was defined as 50% greater improvement from baseline in voiding diary variables. Their analysis revealed 68% of patients with urge incontinence, 56% with urgency frequency and 71% with retention had successful outcomes 5 years following implantation of the pulse generator. However, the authors did not report outcomes pertaining to patient satisfaction, perceived quality of life, or subjective assessment of symptoms.

The authors of the second study seek to determine the long-term effect of sacral neuromodulation on disease specific quality of life and long-term satisfaction in subjects with urinary urge incontinence, urinary urgency, and frequency. Subject demographics, comorbidities, and incontinence parameters (subjective and objective) were then analyzed for potential associations with improved or worsened outcomes.

CHAPTER II

LACK OF ASSOCIATION OF PELVIC OUTLET DIAMETER WITH PELVIC ORGAN PROLAPSE IN SQUIRREL MONKEYS*

II.1 Introduction

Historically, variations in size and shape of the human pelvis have generated¹ hypotheses for the etiology of pelvic floor disorders. The relationship between pelvic organ prolapse (POP) and bony pelvic architecture has been studied in humans to a limited degree (8, 9, 22).

It is well accepted that animal research contributes to the study of human disease by allowing hypotheses to be tested in controlled settings that cannot be performed on humans. Squirrel monkeys have unique characteristics that make them useful for pelvic floor research. For example, 50% of older females demonstrate pelvic support defects (10). As in humans, these pelvic support defects are associated with childbirth and aging (11). Since squirrel monkeys deliver large infants (14% of maternal body weight) relative to maternal size, they are susceptible to pelvic floor injury secondary to labor dystocia. Also, their lifespan is shorter than humans (2 versus 8 decades), which allows

*Reprinted with kind permission from “Lack of Association of Pelvic Outlet Diameter with Pelvic Organ Prolapse in Squirrel Monkeys” Joyce JS, Dornak S, Gendron JM, Reyes M, Ruiz JC, Kuehl TJ, 2014. *International Urogynecology Journal*, Volume 25, 1121-6, Copyright 2014 by Springer.

for serial observation in a research setting. Because of these characteristics, research on squirrel monkey pelvic anatomy contributes to our knowledge-base of POP.

Various modalities for imaging have been used to describe squirrel monkey pelvic anatomy. In 1983, Aksel and Abee (23) used radiographic pelvimetry to evaluate the bony pelvic architecture in females with a focus on predicting the risk of stillbirth in captive breeding programs. Later we used CT imaging to create 3-dimensional models of the bony pelvis of a small series (N = 9) of older animals without detailed obstetric histories (24). In both studies, of the five pelvic dimensions examined as illustrated in Figure 1, only the pelvic outlet diameter was related to stillbirth (23) and prolapse (24).

Recently, magnetic resonance imaging (MRI) has been used to compare levator ani muscle volumes in monkeys with and without prolapse (25), and to compare the effects of delivery (26) and nerve injury (27) on pelvic floor musculature. However, these three articles did not address risk of prolapse in relationship to bony pelvis dimensions. Therefore, despite this research on muscle dimensions and contrast changes, the relationship between pelvic outlet diameter and prolapse in squirrel monkeys has been supported with only the limited observations using CT imaging. Therefore, we undertook this study to use a larger cohort of female squirrel monkeys with known obstetrical histories representing various ages to assess the association between pelvic outlet diameter and POP in the female squirrel monkey.

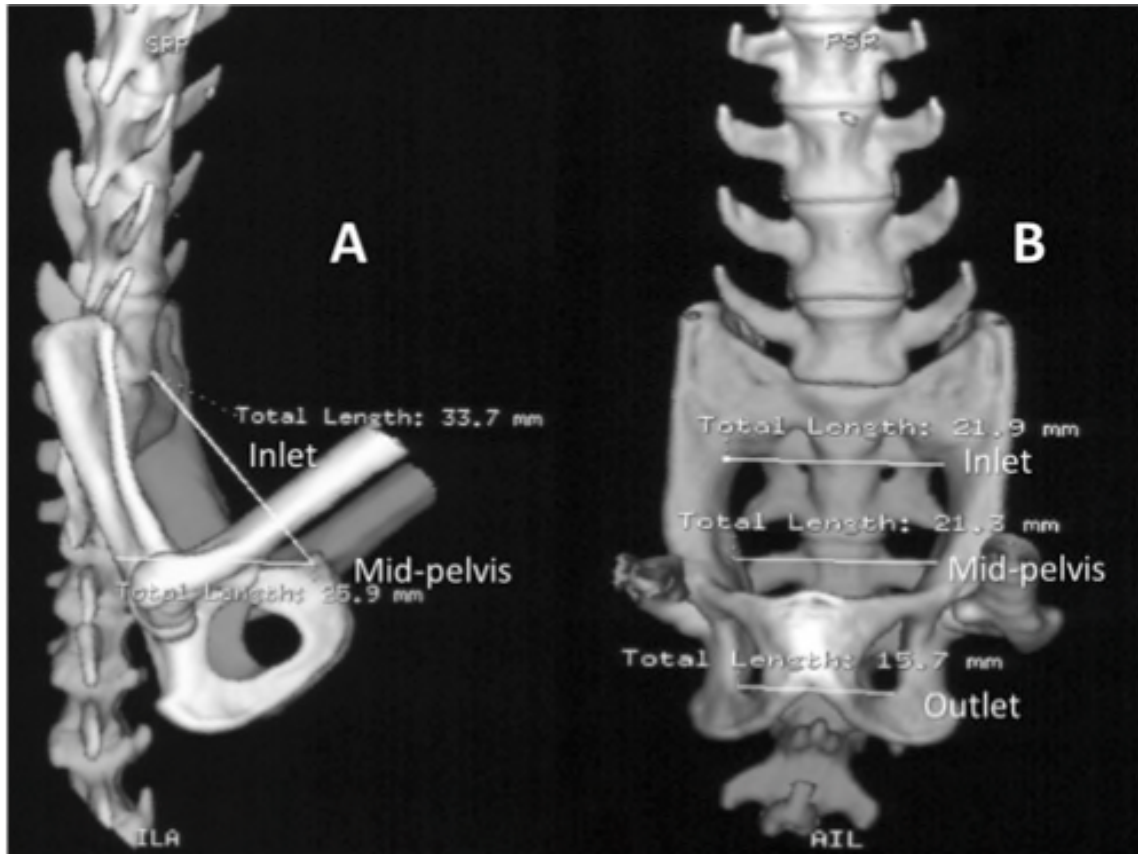


Figure 1. Lateral view (A) of a 3-dimensional reconstruction of the bony pelvis of an adult female squirrel monkey rotated 18 degrees about the spine with measured inlet and mid-pelvis diameters. Anteroposterior view (B) with measured inlet, mid-pelvis, and outlet diameters.

II.2 Methods

Animals. A colony of squirrel monkeys housed at Scott and White Healthcare was used for this study. The use of these animals and MRI methodology was reviewed and approved by the Scott and White Institutional Animal Care and Use Committee.

Nineteen female parous squirrel monkeys with pelvic floor defects based on visual perineal evaluations using methods originally describe by Coates et al. (10) and/or the measured descent of the bladder base to greater than 7 mm below boney pelvic landmarks as defined and illustrated by Pierce et al. (27) were included along with 36 adult females with normal pelvic floor support by both criteria. Animals were of a range of ages, parities, and weights. All animals in the study were initially obtained from the National Squirrel Monkey Breeding and Research Resource now located at the Michale E Keeling Center for Comparative Medicine and Research of The University of Texas MD Anderson Cancer Center in Bastrop, Texas.

Imaging methods. MRI of the pelvic floor was performed on all female monkeys using a previously described technique (25-27). Briefly, animals were sedated, given IV contrast (0.25 mmol/kg of gadolinium chelate as ProHance, Bracco Diagnostics, Inc. Princeton, NJ), and placed inside the MRI unit (3T Siemens Trios, Erlangen, Germany) with their back and legs supported in a natural position inside of an 8-channel wrist coil (model HRW, Philips Medical Systems, Waukesha, WI). Two localizing scans were obtained to set the region of interest for serial images from L7 through C4. A sequence of echo gradient axial images was acquired during a 4.4-minute interval. Images were saved as a DICOM series and transferred to a work station with commercial software (3D-Doctor, Able Software Corp, Lexington, MA), which was used to review, manipulate, and measure the pelvic outlet diameter. The pelvic outlet diameter, as originally defined by Aksel and Abee (23), is the distance between the inferior lateral margins of the obturator foramina at the level of the pubic arch (Figure 2). This is the

only measure of five previously related to development of prolapse (24). Two independent reviewers (JSJ, TJK) performed all measurements in anteroposterior views. Bladder position change relative to a skeletal reference line was measured with a dynamic scan where abdominal pressure is applied using a neonatal blood pressure cuff placed around the animal's abdomen using a previous described technique (26, 27). POP was also directly assessed by an established procedure using perineal visual examination (10).

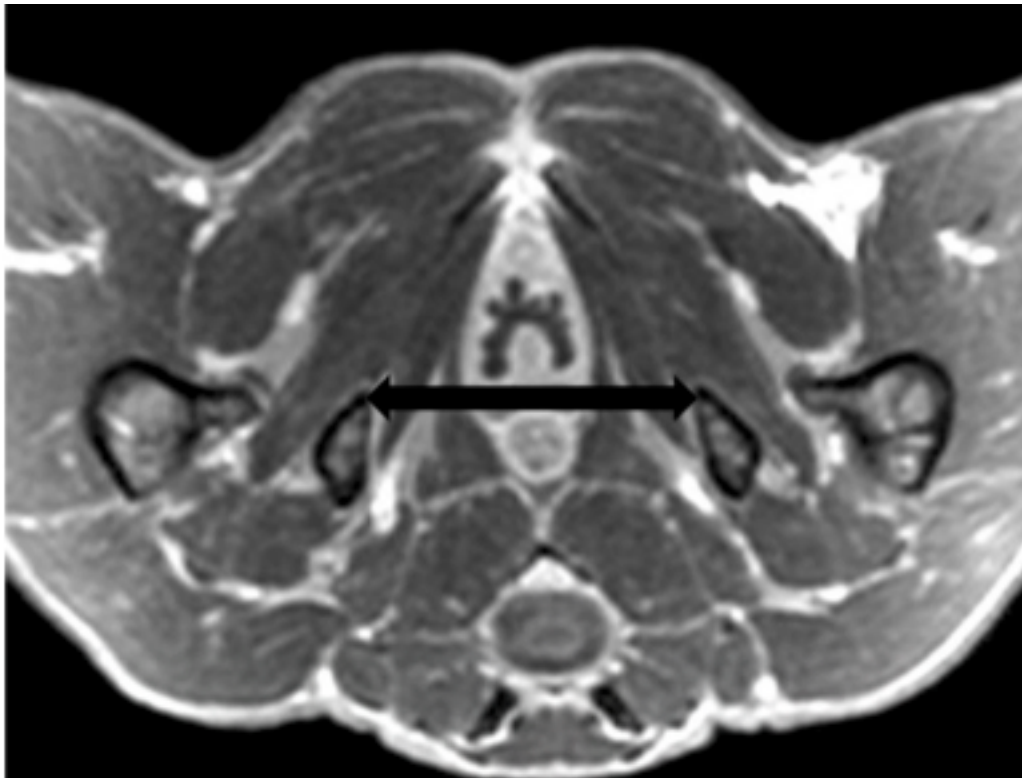


Figure 2. MRI of female squirrel monkey pelvis at level of pelvic outlet diameter. Arrow demonstrates the measured pelvic outlet diameter.

Statistical analysis. Comparison of pelvic outlet diameter measurements by 2 independent observers was made using Cronbach alpha for inter-rater correlation (MediCalc Software, Ostend, Belgium). Prolapse groupings were compared using Student's *t* test for parametric variables. Linear regression analysis examined the relationship of the outlet dimension with age, parity, and weight. Multiple regression analysis examined the relationships of age, parity, and outlet dimension with the presence or absence of POP. These analyses were performed using Statistica software (StatSoft, Tulsa, OK). Receiver operative curve analysis was performed to establish a threshold criterion level for parity as predictor of development of POP (MediCalc Software, Ostend, Belgium). P values less than 0.05 were interpreted as significant.

II.3 Results

The two observers independently performed measurements of 55 pelvic outlet diameters in 55 images independently. The measurements were highly correlated (Cronbach's alpha = 0.96 with a lower 95% confidence limit of 0.94) which imply that there were no differences in measurements between the two observers (Figure 3). Therefore, the average values for the two observers were used for the remaining analyses.

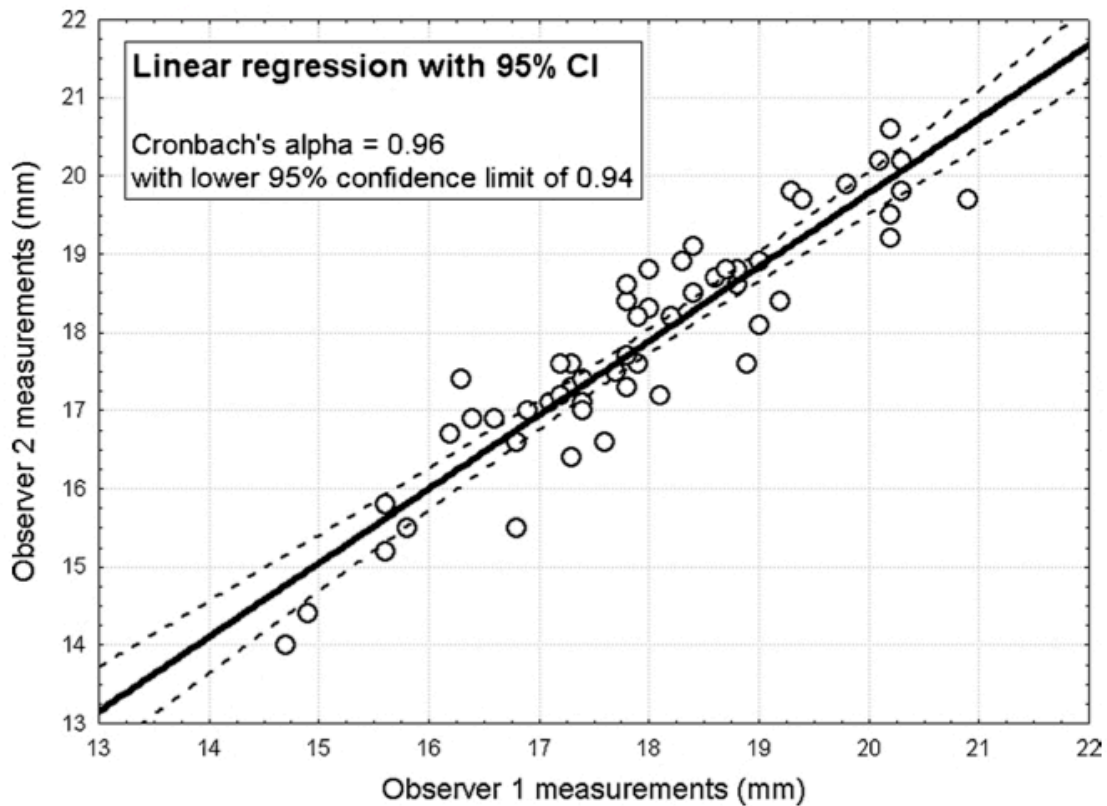


Figure 3. Inter-rater comparison for measurement of pelvic outlet diameter. No difference between observers was found. Linear regression with 95% confidence interval. Cronbach's alpha = 0.96. Lower 95% confidence interval of 0.94.

Table 1 shows independent associations of parity, age, and weight with pelvic outlet diameter in the 55 subjects. The pelvic outlet diameter is not related to parity ($p = 0.10$) or weight ($p = 0.053$), but is inversely related to age ($p = 0.011$). Although weight has a tendency to be directly correlated to the outlet diameter, the effect is small ($r^2 = 0.07$). Figure 4 illustrates the inverse relationship of outlet diameter to age.

Table 1 Relationship between pelvic outlet diameter (POD) and parity, age, or weight

Variable	Correlation	R ²	<i>p</i> value*
Parity	-0.23	0.05	0.10
Age	-0.34	0.12	0.011
Weight	0.26	0.07	0.053

*Multiple regression model

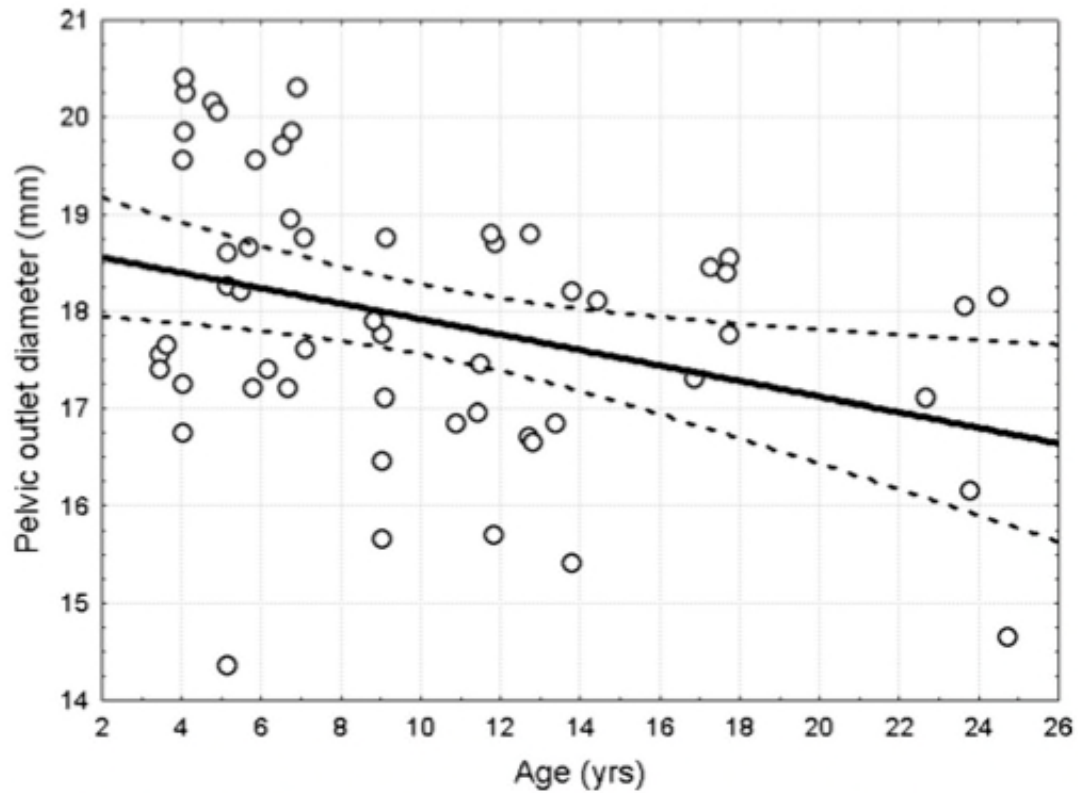


Figure 4. Linear regression with 95% confidence interval comparing the pelvic outlet diameter of 55 animals to ages. Outlet diameter was inversely associated with age. ($p = 0.011$, $r^2 = 0.12$).

Univariate analyses using Student's *t* test demonstrate that animals with POP do not differ from those without POP in regard to age ($p = 0.10$), weight ($p = 0.17$), or pelvic outlet diameter ($p = 0.99$). The two groups do differ in parity ($p = 0.002$ using Student's *t* test). Using multiple regression, only parity demonstrated a significant relationship with POP ($p = 0.007$) (Table 2).

Table 2 Factors related to pelvic organ prolapse in the squirrel monkey

Factor	Animals with POP ($n = 19$)	Animals without POP ($n = 36$)	p level*	p level**
Parity	5.0 ± 2.4	2.3 ± 2.4	0.002	0.007
Age (years)	12.0 ± 5.2	9.2 ± 6.3	0.10	0.99
Body weight (g)	750 ± 63	720 ± 84	0.17	0.08
Outlet Diameter (mm)	17.9 ± 1.2	17.9 ± 1.5	0.99	0.74

*Univariate comparison using Student's *t* tests

**Multiple regression model

Using Receiver-Operator Curve (ROC) methods, parity as a criterion had a significant ($p < 0.0001$) area under the curve (0.78 with 95% CI of .64 to .88) (Figure 5). The optimal criterion for parity as a threshold for prediction of POP was greater than 2 vaginal deliveries (sensitivity of 64% and specificity of 89%); however, greater than 1 vaginal delivery has a similar sensitivity (61%) and the same specificity (89%).

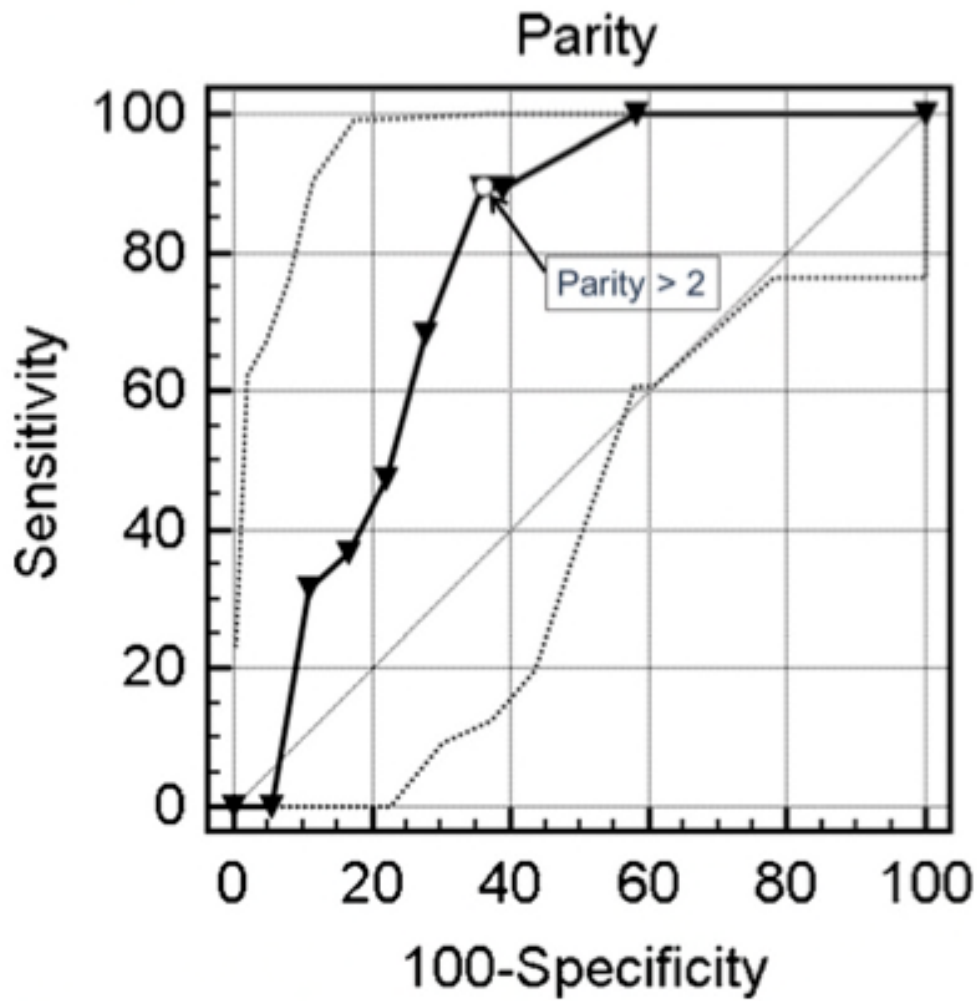


Figure 5. Receiver-operator curve with 95% confidence interval for analysis of the threshold number for parity in relation to pelvic organ prolapse in a cohort of 55 adult squirrel monkey females. Optimum criterion point (open circle) is for parity greater than 2.

II.4 Discussion

As previous observations in squirrel monkeys supported the concept that of five boney pelvis measurements, only the pelvic outlet diameter in the anterioposterior

dimension can identify animals with a higher frequency of stillbirths (23) and POP (24), we anticipated that this trial would confirm the risk conferred by a smaller pelvic outlet for development of POP. As illustrated in Figure 6, the fetal face is the presenting part as the majority of squirrel monkey deliveries are mentum anterior (28). However, in the current trial, only parity was related to the development of POP. Our study in squirrel monkeys showed that pelvic outlet diameters do not differ between animals with and without prolapse, which is consistent with the findings by Stein et al. (22). Stein et al. studied bony landmarks at the level of the pelvic floor in white women and found no association between outlet dimensions and POP (22).

We also reaffirmed earlier observations that parity appears to be the most significant risk factor for prolapse development in squirrel monkeys (11). However, in the previous study of a breeding colony, parity and age were highly associated, so that it was not possible to distinguish which of these characteristics might have the strongest effect. In our current study, age, weight, and outlet diameters were not associated with prolapse, suggesting that parity is the primary risk factor. In spite of a preliminary trial with a cohort of 9 older animals (24), the pelvic outlet diameter for animals with prolapse in the current study was the same as for animals without prolapse (17.9 ± 1.2 and 17.9 ± 1.5 mm, respectively). The measurements made by the two independent observers were precise and valid for this analysis.

The inverse relationship between age and pelvic outlet diameter is unexplainable at this time. It is possible that the older animals in this cohort had smaller pelvises to begin with, suggesting that the younger animals benefited from improved nutrition in

their captive environments. It is also possible that pelvis measurements might change with age. The later hypothesis is testable in the future by examining serial measurements in animals followed for an extended interval. Although animal weight had a tendency to be correlated to outlet diameter, the effect was small.

The advent of sensitive radiographic technology has enticed researchers to study bony pelvic architecture in humans in hopes of addressing various hypotheses pertaining to risk of development of pelvic organ prolapse. Using computed tomography, Sze et al. found that women with prolapse had larger transverse inlet diameters than women without prolapse (9). Using MRI, Handa et al. found that a wider transverse inlet and a shorter obstetrical conjugate were significantly associated with pelvic floor disorders (8). In previous studies of five measures of the pelvic inlet and outlet in squirrel monkeys, only the pelvic outlet diameter was found to be related to stillbirth using radiographic projection (23) or POP using CT (24) in a small series of older animals. In squirrel monkeys, the ilium is longer and narrower and the outlet faces more dorsally (Figure 6). The fetal head does not simultaneously pass the sacral promontory and pubic symphysis, so some of the classically defined pelvic diameters may not be relevant to this species (29). There are no ischial spines as in the human pelvis. The fetal head does become bound circumferentially by maternal bony pelvis when it reaches the plane of the second sacral vertebra and the superior ramus of the pubic symphysis until it exits at the outlet position (29). The smallest of the measured diameters is the outlet (10, 24), so while this restriction would seem to be the most important, our study did not support this hypothesis.

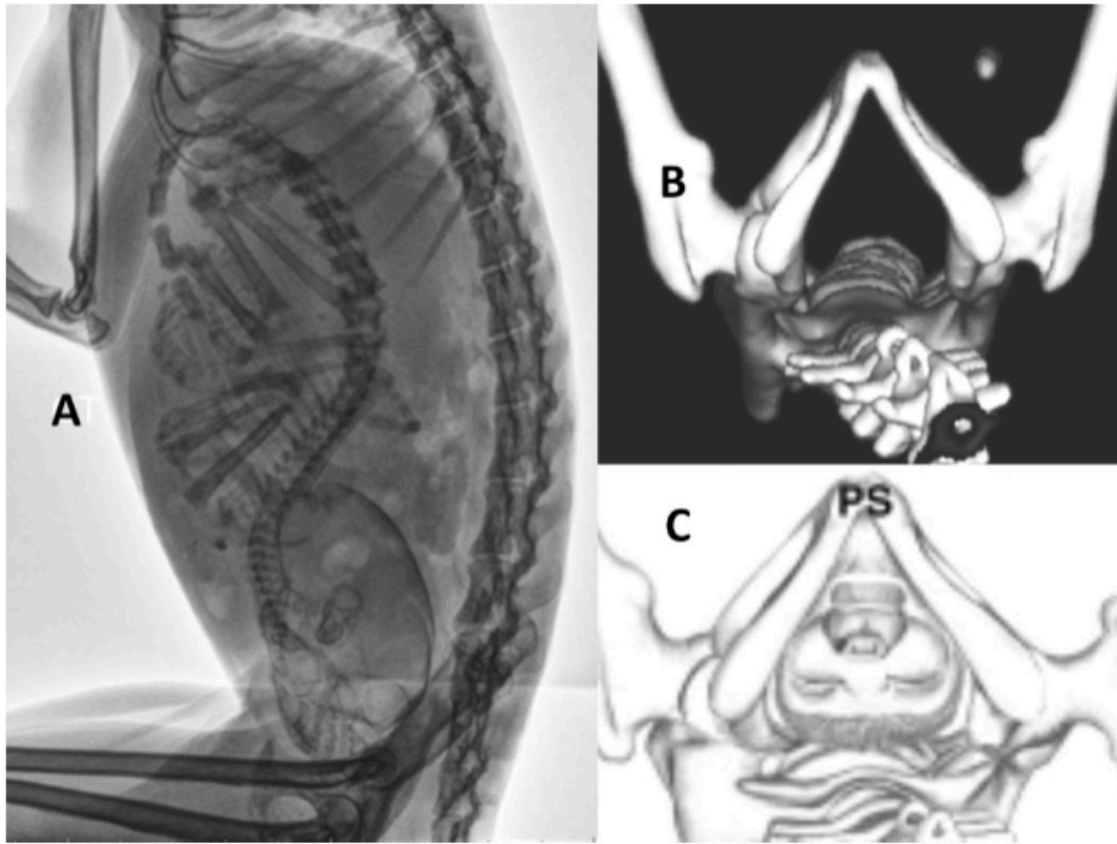


Figure 6. Lateral radiograph of squirrel monkey fetus entering the birth canal (A), axial view of 3 dimensional reconstruction of CT scan with tail in front (B), and artist depiction of mentum anterior presentation (C) to demonstrate that anteroposterior outlet dimension represents a restriction for squirrel monkey vaginal delivery.

It was the initial dilemma of impaired reproductive performance in captivity secondary to a high perinatal mortality rate that encouraged investigators to develop pelvimetry methods as a predictor of pregnancy outcome (23). This finding led to hypotheses associating traumatic pelvic floor injury from labor dystocia with subsequent prolapse. Despite the suggested relationship between a small pelvic outlet diameter and

prolapse in an earlier and smaller cohort of squirrel monkeys (23), the currently study provides data from a different and larger cohort that does not support the earlier preliminary findings. Further investigation of pelvic organ prolapse etiology with a focus on the role of pregnancy and delivery in squirrel monkeys is warranted and in progress

CHAPTER III

LONG-TERM ASSESSMENT OF PATIENT SATISFACTION AND QUALITY OF LIFE FOLLOWING SACRAL NEUROMODULATION FOR THE TREATMENT OF URINARY URGE INCONTINENCE, URGENCY AND FREQUENCY

III.1 Introduction

Sacral neuromodulation (*InterStim®*, Medtronic, Inc., Minneapolis, MN) first received FDA approval for the treatment of urinary urge incontinence in 1997, then later received approval for the treatments of urinary urgency, frequency and non-obstructive urinary retention in 1999. Since then, several studies have evaluated its long-term cure and efficacy rates. A 5-year prospective multicenter trial evaluating long-term safety and efficacy in patients who received sacral neuromodulation for refractory urge incontinence, urgency frequency, and retention demonstrated 5-year post-implantation success rates of 68%, 56%, and 71% for urge incontinence, urgency frequency, and retention respectively (21). In this study, the researchers defined clinical success as objective symptom improvement measured by voiding diaries. Although they did attempt to address patient quality of life by using the Short Form-36 and Beck Depression Inventory, these instruments are more indicative of patient overall general health rather urinary incontinence or voiding dysfunction.

In an effort to evaluate sacral neuromodulation's effect on patient satisfaction and quality of life at least 1-year remote from *InterStim®* placement, Foster et al (30)

prospectively evaluated 52 patients with refractory urge incontinence with a satisfaction survey and the IIQ short form. Investigators discovered that 84% of respondents were still satisfied with *InterStim*® treatment at an average interval of 27 months. Satisfied subjects also demonstrated a significantly greater improvement with 24-hour pad weights during test stimulation than dissatisfied subjects, 85% versus 60% respectively. However, improvement in daily pad usage during test stimulation was not predictive of subject satisfaction.

The purpose of this study is to measure long-term satisfaction of women treated with sacral neuromodulation for refractory urinary urge incontinence, urinary urgency, and frequency. Subject demographics, comorbidities, objective incontinence parameters, and scores from symptom severity and disease related quality of life questionnaires were analyzed for potential associations with improved or worsened outcomes.

III.2 Methods

This was a prospective study approved by the University of Missouri Health Sciences institutional review board (IRB). Subjects were included if they were implanted with *InterStim*® (Medtronic, Inc.) sacral neuromodulator for the treatment of urinary urge incontinence or urinary frequency and urgency between July 1, 2007 and August 30, 2010. Subjects were excluded if they were non-English speaking or serving a prison sentence. All subjects received their care from a single female pelvic medicine

and reconstructive surgery (FPMRS) physician at a large mid-western university hospital. Subject demographics were collected from an IRB approved, continuous, prospective surgical database. The subject's medical history, physical examination, and scores from the Urogenital Distress Inventory-6 (UDI-6) and Incontinence Impact Questionnaire-7 (IIQ-7) validated questionnaires, recorded at the time of the initial evaluation for their urinary complaint, were collected from the subject's electronic health record. In addition, objective incontinence parameters (24-hr pad weight, daily pad usage [number of pads], and a 3-day bladder diary to document leakage episodes per day) recorded both before and during test stimulation, were collected from the patient's electronic health record.

All subjects underwent a test stimulation period of 6 to 8 days using the first stage lead placement (FSLP) with the tined lead technique. The technique for FSLP and permanent device implantation has been previously described (31, 32).

The subjects who proceeded to Stage II implantable pulse generator (IPG) placement were identified and contacted by either telephone or electronic mail for interview.

Telephone contact attempts were made until the subject or caregiver answered the phone, or if the telephone company verified a non-working number. A version of the interview was sent to the subject or her caregiver if that was her desired method of contact. If the subject underwent lead placement revision or removal of IPG, the time interval between placement and revision/removal as well as its indication were recorded. The subject's past medical history was then reviewed and updated to account for the acquisition/development of any acute or chronic medical illness.

The primary outcome of the analysis was to measure long-term satisfaction, including perceived level of improvement, symptom severity and disease related quality of life in subjects who underwent sacral neuromodulation for the treatment of urinary urge incontinence, urinary urgency, and frequency. Subject satisfaction was assessed by using a Likert-type scale and direct “yes” or “no” questions. A Patient Global Impression of Improvement test was used to assess the subject’s perceived level of improvement of their urinary symptoms. Symptom severity and disease related quality of life at the time of interview were assessed using the UDI-6 and IIQ-7 questionnaires. Subjects were also asked questions about daily pad usage, additional treatment sought for their urinary symptoms, and whether or not they would receive *InterStim*® treatment again in retrospect (Table 3). Subjects were then queried on their last follow-up appointment for IPG assessment, their last evaluation for urinary tract infection, and whether or not they had symptoms of constipation (straining, hard stools, fewer than 1 bowel movement a day). Finally, dissatisfied subjects were asked why they believed their *InterStim*® was not producing satisfactory treatment results.

The secondary outcome of the analysis was to identify any associations between preoperative variables (medical history, examination, UDI-6 and IIQ-7 scores, and the pretest and test phase objective incontinence parameters) and long-term subject satisfaction. In addition, subject UDI-6 and IIQ-7 scores recorded at the time of interview, were compared to UDI-6 and IIQ-7 scores recorded at the time of the subject’s initial evaluation.

Table 3 Questions assessing patient satisfaction at time of interview

<i>Compared with before you received the InterStim[®] treatment, do you feel</i> <ol style="list-style-type: none">1. Much better2. Somewhat better3. No different4. Somewhat worse5. Much worse
<i>Compared with before you received the InterStim[®] treatment, what percentage improvement have you experienced? (Scale of 0-100)</i>
<i>If you had to do it over again, would you choose the InterStim[®] treatment?</i> <ol style="list-style-type: none">1. Yes2. No
<i>Are you satisfied with your InterStim[®] treatment?</i> <ol style="list-style-type: none">1. Yes2. No
<i>How many pads do you use on an average day?</i>
<i>Have you sought any additional therapy for your urinary symptoms?</i> <ol style="list-style-type: none">1. Yes2. No

Table 3 Continued

If “yes” to the above questions, then what treatments did you receive?

1. Physical rehabilitation
2. Medication
3. Botulinum toxin injection
4. Other

Comparisons of UDI-6 and IIQ-7 scores, daily pad usage, and the number of recorded leak episodes per day before *InterStim*® placement and at time of final interview were made by paired Wilcoxon signed rank tests. Response levels to individual questions on the UDI-6 and IIQ-7 surveys were dichotomized as “not at all” as equivalent to “no”, while “slightly”, “moderately”, and “greatly” were recorded as “yes”.

Proportions of subjects with various characteristics before treatment and at the final interview were compared by Chi-square or Fisher exact tests as appropriate. Data were compared between satisfied and not satisfied subjects using one-way analysis of variance (ANOVA) for normally distributed variables, and by Kruskal-Wallis One-Way ANOVA on Ranks for non-normal variables. Results were reported as percentage of subjects; means with 95% confidence intervals of the means for treatment comparisons of normally distributed variables; and medians with 95% confidence intervals of the median for non-normal data.

III.3 Results

Forty-six subjects with refractory urinary urge incontinence and frequency and urgency underwent test stimulation for sacral neuromodulation between July 1, 2007 and August 30, 2010. Forty-two of these subjects had successful test stimulation, proceeded to stage II IPG placement, and therefore met inclusion criteria. The median age of these subjects was 67 (range 17-88) years at the time of IPG placement.

Of the forty-two subjects eligible for telephone interview, 24 (52%) were contacted and provided responses. One subject was contacted but unable to answer questions secondary to her advanced dementia. One subject was contacted but declined the interview. Eight subjects were deceased, and 8 subjects did not respond to telephone calls or email requests (Figure 7). The median time interval between IPG placement and follow-up interview was 51 months (range 39 to 59 months).

Among the 24 subjects who were contacted and provided responses, 22 (92%) were treated for refractory urgency incontinence and 2 (8%) were treated for urgency/frequency syndrome. Five of these 24 subjects had their IPG removed secondary to loss of efficacy. Overall, nine (37.5%) of the 24 subjects who were contacted and provided responses were “satisfied” with *InterStim*® therapy, and 12 (50%) stated that they would “do it all over again” (Figure 7).

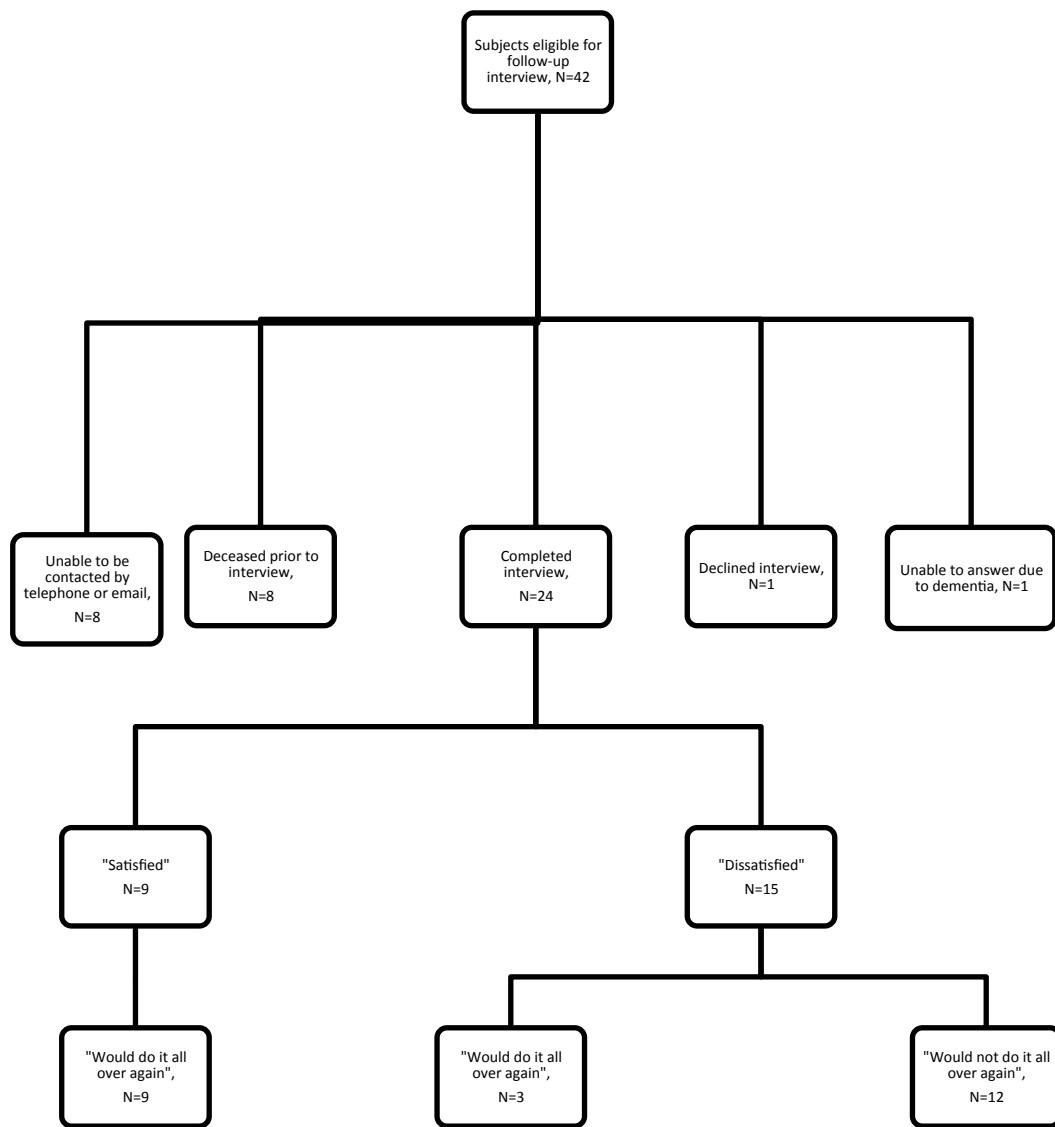


Figure 7. Subject flow chart

Satisfied subjects reported a 50% median improvement [Likert-type scale] of their urinary symptoms compared to before receiving *InterStim*®. Satisfied subjects were younger (Table 4) than dissatisfied subjects at the time of IPG placement (mean 51 vs. 67; $p = 0.01$). One subject, who was 17 years old was excluded from the age analysis because her age was lower than the average by more than three standard deviations.

Table 4 Comparison of patients satisfied and dissatisfied at long-term follow-up with respect to preoperative characteristics and incontinence parameters

Patient characteristic or incontinence parameter	Dissatisfied (n = 14)		Satisfied (n = 9)		<i>p</i>
Age ^a (years)	67	(62 - 72)	51	(37 – 65)	0.010
Pad usage ^a (pads/day)	3.3	(1.9 – 4.7)	3.3	(0 – 2.5)	1.0
24 hr pad weight ^b (g)	219	(113 – 379)	165	(34 – 554)	0.69
Incontinence episodes ^b (episodes/day)	2.8	(1.0 – 7.3)	3.2	(0 – 7.0)	0.39

^a Data are mean (95% confidence interval) with *p* values derived from one-way ANOVA.

^b Data are median (95% confidence interval) with *p* values derived from Kruskal-Wallis One-Way ANOVA on Ranks

At the time of follow-up interview, satisfied subjects demonstrated lower UDI-6 scores ($p = 0.0014$, lower IIQ-7 scores ($p = 0.033$), greater symptom improvement ($p = 0.00022$), and were wearing fewer pads per day (1.0 vs. 4.0, $p = 0.0030$) for protection compared to dissatisfied subjects (Table 5). Likewise, subjects who would “do it all over again” had both lower UDI-6 scores ($p = 0.071$), lower IIQ-7 scores ($p = 0.030$) and wore fewer pads (1.3 vs. 3.8; $p = 0.019$) compared to those who would not “do it all over again.”

Table 5 Comparison of patients satisfied and dissatisfied at long-term follow-up with respect to postoperative (test phase) and long-term incontinence parameters and survey scores

Patient characteristic or incontinence parameter	Dissatisfied (n = 14)		Satisfied (n = 9)		<i>p</i>
Postoperative follow-up ^a (months)	50	(46 – 54)	51	(46 – 56)	0.61
Postoperative change in pad weight ^{b,c} (percentage reduction)	80%	(36 – 100)	93%	(0 – 100)	0.22
Postoperative change in daily pad usage ^{b,d} (pads/day reduction)	2.0	(0 – 4.0)	4.0	(0 – 6.0)	0.43
Long-term reduction in daily pad usage ^{b,e} (pads/day reduction)	1.0	(-1.0 – 2.0)	-1.8	(-6.0 – 0)	0.017
Long-term reduction in UDI-6 score ^{a,e}	14	(-11 – 29)	40	(5.5 – 65)	0.11
Long-term reduction in IIQ-7 score ^{b,e}	14	(-24 – 29)	43	(-38 – 86)	0.11

^a Data are mean (95% confidence interval) with p values derived from one-way ANOVA.

^b Data are median (95% confidence interval) with p values derived from Wilcoxon Signed-Rank Test for Difference in Medians

^c (24-hr pad weight before test stimulation - 24-hr pad weight during test stimulation)/(24-hr pad weight before test stimulation)

^d (Value before test stimulation) - (value during test stimulation)

^e (Value before test stimulation) - (value at long-term follow-up)

Dissatisfied subjects were more likely to report urinary frequency (93% vs. 56%; $p = 0.047$), urinary urge incontinence (100% vs. 67%; $p = 0.042$), and stress urinary incontinence (87% vs. 33%; $p = 0.021$). Dissatisfied subjects were significantly more likely than satisfied subjects to report that their symptoms affected their ability to perform housework (53% vs. 0%, $p = 0.0095$), exercise ($p = 0.033$), enjoy entertainment activities ($p = 0.036$), and travel by car or bus for a distance greater than 30 minutes from home (73% vs. 22%; $p = 0.033$). Subjects who stated they would “do it all over again” were less likely to report that their symptoms affected their ability to perform housework, (8.3% vs. 58%; $p = 0.027$), exercise (33% vs. 75%; $p = 0.041$), and enjoy entertainment activities (42% vs. 83%; $p = 0.089$). No difference between satisfied and dissatisfied subjects, respectively, was found regarding the median time interval in months since their last IPG evaluation (16 vs. 31; $p = 0.46$) or their last screening for urinary tract infection (12 vs. 12; $p = 0.67$). Dissatisfied patients were no more constipated than satisfied patients (38% vs. 57%; $p = 0.64$).

When dissatisfied subjects were asked why they thought their *InterStim*® was not working, 2 stated that the *InterStim*® did not meet their expectations, and they were therefore not interested in seeking follow-up. One subject thought that the IPG needed re-evaluation, but was unable to return for a follow-up visit due to lack of transportation. One subject could not provide an explanation for why they were dissatisfied, and one subject declined to provide an answer. Finally, the percentage of dissatisfied subjects who reported they sought additional treatment did not significantly differ from satisfied subjects (14% vs. 22%; $p = 1.0$).

Satisfied subjects did not differ from dissatisfied subjects in their past medical history before *InterStim*® treatment nor at time of the follow-up (proportion with pelvic organ prolapse, menopause, hysterectomy, diabetes mellitus, hypertension, heart disease, lung disease, low back pain, GI disease, headaches, neurological diseases, blood clots, and/or kidney disease). They also were similar in their obstetrical history (parity, vaginal deliveries, cesarean deliveries, largest baby, obstetrical laceration or trauma). Satisfied subjects did not differ from dissatisfied subjects with their objective voiding parameters (24-hour pad weight, daily pad usage, and number of leak episodes as documented on a 3-day bladder diary) recorded before the test stimulation phase or in post-void residual measured at that time (Table 4). Satisfied subjects demonstrated less long-term reduction in daily pad usage.

III.4 Discussion

This study describes long-term satisfaction, symptom severity, and disease related quality of life in patients receiving sacral neuromodulation for the treatment of urinary urge incontinence, and urinary frequency and urgency. We found that 37.5% of the 24 subjects who responded were still satisfied with sacral neuromodulation after a mean interval of 51 months, and 50% of those who responded affirmed they would “do it all over again.” This represents a dramatic decline in treatment satisfaction and willingness to repeat the procedure compared to the results reported by Foster et al (30) at 27 months in which 84% of respondents were satisfied and 80% would “do it all over

again”. Our rates of satisfaction resemble those reported in a prospective follow-up study by Bosch and Growen (33). They found that after 48 months, 18 (40%) of the patients were “cured,” and another 9 (20%) were considered “partially cured” at 48 months. These investigators defined treatment cure as a 90% reduction in pad use and/or incontinence episodes, while partial treatment cure was defined as a 50% to 90% reduction in pad use and/or incontinence episodes.

Satisfied subjects in our study were on average 16 years younger at time of *Interstim*® IPG placement than dissatisfied subjects (Mean \pm SEM: 51 \pm 6.2 vs. 67 \pm 2.3 years; $p=0.010$). The association between age and successful outcomes has been demonstrated before, in a 29 month prospective follow-up of 55 patients by Amundsen (34) and in which individuals younger than 55 years had a statistically significant greater cure rate (65% vs. 37 %). This same study concluded that having three or more chronic conditions was associated with a lower cure rate in both younger and older individuals, and found that patients with neurologic conditions have lower cure rates. Although we speculate that depression has a profound effect in patient’s perceived level of satisfaction, we did not believe we were capable of reporting accurate rates of this particular comorbidity without proper screening to capture undiagnosed cases within the cohort.

We were not able to demonstrate any correlation between performance on objective test phase parameters and long-term satisfaction, unlike Foster et al. who found a significant association with improvement (84%) on 24-hour pad test weight during test stimulation and patient satisfaction and desire to “do it all over again” after 27 months.

Our lack of finding an association is consistent with results previously reported (32, 34-36).

We do not believe that the lack of association between improvement demonstrated on objective voiding parameters (24-hour pad weight, 3 day bladder diary and pad usage) during test stimulation invalidates their use for screening eligible patients for IPG placement, as we were underpowered to detect these associations. Clearly, patients need to demonstrate some level of improvement prior to undergoing implantation of a permanent and expensive treatment modality. However, other factors must be incorporated in calculating estimated long-term efficacy. The ability to convey accurate and realistic expectations will be paramount to patient satisfaction. Even with less than optimal improvement patients can still experience satisfaction if appropriate expectations are established. Perhaps, a long-term efficacy/satisfaction prediction model may be created similar to the one constructed to estimate the risk of *de novo* stress urinary incontinence after vaginal pelvic organ prolapse surgery (37).

We were unable to demonstrate associations between subject satisfaction and constipation, time interval since last IPG evaluation, and time interval since last check for a urinary tract infection. However, differences were present, and these differences may have been significant with higher power. Associations amongst these variables would imply that subject satisfaction with sacral neuromodulation depends on patients taking ownership of their disease and being pro-active in managing their health. This includes pro-actively managing their bowel function, and being self-motivated to seeking evaluation for possible urinary tract infections and seeking evaluation of their

IPG. The 2 dissatisfied subjects who reported that their *InterStim*® “did not meet their expectations, and were therefore not interested in seeking follow-up” did not return for IPG re-evaluation after the stage II procedure. It is reasonable to argue that successful outcomes, and therefore patient satisfaction with sacral neuromodulation, depends on how well the patient cares for his or herself and complies with scheduled maintenance for their IPG.

The 37.5% satisfaction rate further illustrates the challenge in treating urinary urge incontinence, frequency and urgency. Despite this relatively low level of reported subject satisfaction at 53 months, it still represents an improvement over anticholinergic therapy when one considers the high rates of discontinuation of these drugs due to perceived ineffectiveness and side effects (38).

Strengths of the study include the prospective design and use of validated questionnaires. Several weaknesses need to be addressed. First of all, there was a limited cohort size (41) and a limited number of subjects (24) providing responses for the long-term follow-up interview, which makes it difficult to draw conclusions. Second, we did not distinguish patients who may have had mixed urinary incontinence in our analysis, as this may have resulted in a difference in satisfaction. Future studies should include a cohort sufficiently large to account for the large number of patients lost to follow-up or deceased. Because of the telephone interview format, we were unable to report performance and objective parameters such as the 3-day bladder diary and 24-hour pad weight. This prevented us from describing associations between reported subject satisfaction and these parameters. Furthermore, we were unable to assess long-

term satisfaction of sacral neuromodulation for treating non-obstructive urinary retention because we had no patients that met criteria. Future studies should include the ability to accurately account for depression.

In conclusion, after a mean follow-up interval of 51 months, 37.5% of subjects still reported being satisfied with sacral neuromodulation for the treatment of urinary urge incontinence and urinary urgency and frequency, while 50% reported they would “do it all over again.” Except for younger age, statistical analysis of multiple factors did not reveal predictive variables for patient satisfaction or willingness to repeat the therapy. Given the small cohort study available for telephone interview (24 subjects) further studies with a larger cohort size are needed to identify predictive variables for clinical success, correlate duration of disease with clinical efficacy and patient satisfaction, and to determine differences in patient follow-up and reprogramming between satisfied and non-satisfied patients.

CHAPTER IV

FUTURE DIRECTIONS AND CONCLUSIONS

IV.1 Future Directions

The pelvic floor muscles—pubococcygeous-puborectalis complex-- interact with connective tissue to provide the primary support for the pelvic organs by countering intra-abdominal and gravitational forces applied to the vagina through constant muscle tone (14, 39). Pelvic floor weakness secondary to neuropathic injury or mechanical muscular damage results in the endopelvic fascia becoming the primary mechanism of support, eventually leading to loss of normal anatomic position through breaks and attenuation of this support.

Clinical research and imaging studies of the pelvic floor have demonstrated the effects of childbirth on pelvic floor musculature (39). The levator hiatus, which is defined by the puborectalis and pubococcygeus muscles and pubic bone, is considered to be the largest hernia portal in the human body (40). It has been studied in humans using both MRI (41) and ultrasound technology (40, 42). In human studies using 3D and 4D ultrasound imaging, hiatal dimensions have been observed to be larger with age (43), parity (44) and vaginal childbirth (45). In addition, larger hiatal dimensions have been observed in women with greater pelvic organ descent (40).

Using MRI, Handa et al assessed human pelvic anatomy and pelvic floor disorders 6-12 months following delivery (41). The investigators designated the

pubococcygeal line to be the normal location of the pelvic floor and defined the genital hiatus as the distance from the inferior posterior aspect of the symphysis to the posterior rectal wall at the anorectal junction in the most cranial mid-sagittal image that included the symphysis. They did not observe differences in soft tissue dimensions between women with and without pelvic floor disorders, including anterior vaginal prolapse.

Because the squirrel monkey has established its self as an experimental model that is useful for studying pelvic organ prolapse in humans (10, 11), future studies describing the soft-tissue anatomy of the genital hiatus and pelvic floor in this species should be pursued. Once this anatomy has been described, then experiments seeking to determine associations between soft-tissue dimensions of the genital hiatus and pelvic floor and the development of pelvic organ prolapse in squirrel monkeys can and should be performed. As described earlier, the boney pelvic outlet diameters in squirrel monkeys were assessed for associations with pelvic organ prolapse (46). If associations between hiatal dimensions and age, parity, mode of offspring delivery, and prolapse are found to be similar between squirrel monkeys and humans, hypotheses built on intervention for preventing pelvic organ prolapse can be performed in monkeys that cannot be performed in humans. Future studies should seek to determine the association of prolapse, age, parity, and mode of delivery on hiatal dimensions in squirrel monkeys. This would further validate the squirrel monkey as an animal model, and therefore enable testing hypotheses that involve interventions.

IV.2 Conclusions

Human pelvic floor disorders have and will continue to pose a significant medical challenge to our health system. Research aimed at further determining risk factors for the development of pelvic organ prolapse and urinary incontinence will not only enhance our understanding the disease, but more importantly help us formulate hypothesis directed at interventions that may prevent their onset and progression. Animal models such as the squirrel monkey will have influential roles in the experimental design of future studies seeking to determine the effectiveness of hypothetical interventions. Innovative therapies such as sacral neuromodulation (*InterStim®*, *Medtronic, Inc., Minneapolis, MN*) will require vigorous studies to determine their effectiveness in treating disease and therefore its usefulness to our health system. It will be imperative that future research design incorporates a combination of domains including subjective assessment of symptoms, objective quantification of symptoms, clinician's observations and examination, improvements in quality of life, and any socioeconomic measures, in order to draw meaningful conclusions to the value of that particular treatment.

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